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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,009	03/28/2005	Constantin G. Ioannides	UTSC:711US/10410987	7673

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

NOTIFICATION DATE	DELIVERY MODE
09/16/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/507,009	IOANNIDES ET AL.	
	Examiner	Art Unit	
	MARIANNE DIBRINO	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,20-25 and 44-56* is/are pending in the application.

4a) Of the above claim(s) *25,44,48-50 and 52-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,20-24,45-47,51 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/15/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and response filed 7/1/10 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election without traverse of Group I and species of SEQ ID NO: 11 (KIFGSLA-iso-Phe-L), as well as "an increase in the antigen's ability to protect CTL's from activation induced cell death" as the species of "modulation of immunity" in Applicant's amendment and responses filed 7/20/07 and 7/28/08. The Examiner notes that SEQ ID NO: 11 has the unnatural amino acid residue iso-Phe at position 8 (P8). Iso-Phe differs from Phe in that iso-Phe lacks the CH_2 group between the phenol ring and the peptide bond.

Upon consideration of Applicant's newly filed IDS reference cited below, the species of norvaline recited in instant claim 45 is included in examination.

Claims 8, 20-24, 45-47, 51 and newly added claim 56 are presently being examined.

3. Applicant's amendment filed 7/1/10 has overcome the prior rejection of record of claim 27 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

4. Applicant's amendment filed 7/1/10 has overcome the prior rejection of record of claim 27 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

5. Applicant's amendment filed 7/1/10 has overcome the prior rejection of record of claims 4, 5, 8, 14, 15, 20-24, 26-29, 31, 46, 47 and 51 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

6. Applicant's amendment filed 7/1/10 has overcome the prior rejection of record of claim 27 as it recites the limitation "wherein modulation of immunogenicity comprises an increase in the antigen's ability to activate low-avidity CTLs" at lines 1-3, as lacking antecedent basis.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 8, 20-24, 45-47, 51 and 56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This is a new ground of rejection necessitated by Applicant's amendment filed 7/1/10.

The specification does not disclose how to make and use the instant invention, a method for preparing a composition comprising a peptide antigen, said method comprises obtaining a peptide antigen comprising a CTL epitope, wherein the CTL epitope comprises one or more non-natural amino acid residues selected from the recited residues, and including the limitations of the dependent claims.

The specification has not enabled the breadth of the claimed invention because the claims necessarily encompass substituting or adding one or more of the recited non-natural amino acid residue(s) to a peptide that is or is not already a CTL epitope in order to obtain a peptide antigen, since the amino acid residues recited are non-naturally occurring residues that are not present in peptides.

The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed method can be used.

The instant specification discloses that the E75 tumor associated peptide was modeled in the HLA-A2 class I MHC peptide binding groove, the position(s) in the peptide to be substituted was/were determined, certain peptide analogs were created with single amino acid substitutions (non-natural residues) at certain positions in the peptide in order to add one, two or three CH2 groups or to remove one CH2 group, the peptide analogs were evaluated for ability to induce different cytokines such as IFN-γ or IL-2, CTL tested for cross-reactivity against the wild-type peptide. The results disclosed in the specification indicate that different analogs behaved differently with regard to cytokine induction, cross-reactivity, peptide-induced CTL lytic activity, and that yields of high affinity CTL were influenced (higher yields) by the degree of attenuation of TCR signaling using less CH2-extended analogs. It is noted that the P4, P7 and P8 positions of the nonamer peptide were altered, these residues pointing either sideways or upwards with respect to the MHC class I peptide binding groove (see Example 1).

Thus, the specification teaches selecting the amino acid residue to be substituted by the position it occupies in a peptide (that is already known to be a CTL epitope), the direction of its side chain orientation relative to the peptide binding groove of MHC class I, and the nature of the amino acid residue at the position to be substituted, in order to determine if the amino acid residue can potentially be substituted with a non-natural amino acid residue, and what the nature of that substitution might be, in order to influence such properties as cytokine induction, cross-reactivity, peptide-induced CTL

lytic activity and affinity. The specification also teaches actually assessing these indices for the E75 peptide to determine if it is a still a peptide antigen.

The specification does not disclose a method that adds one or more of the recited non-naturally-occurring amino acid residues to a CTL epitope, wherein the non-natural amino acid residues are flanking the amino acid sequence consisting of the CTL epitope.

Evidentiary reference Rodkey teaches that an antigen is an agent that binds specifically to preformed antibodies or T cells, while an immunogen is an agent that is capable of inducing an immune response (see page 5). Rodkey teaches that CTL epitopes are linear, while antibody epitopes may be either linear or conformational (*i.e.,* in the latter the amino acid residues forming the epitope may be non-contiguous, not close together and the epitope may be dependent upon a correct three dimensional configuration of the entire peptide or polypeptide) (see page 15).

The instant claims are drawn to a method for preparing a composition comprising a peptide *antigen (i.e., the peptide antigen must bind specifically to preformed T cells or antibodies)*, wherein one or more of the recited non-natural amino acid residues may be substituted in or added to a peptide that is or is not a CTL epitope.

It is unpredictable, except for the E75 tumor associated peptide, which amino acid residues in or flanking a CTL epitope peptide (or any other non-CTL epitope peptide to make it a CTL epitope) can be altered to substitute or add one or more of the recited non-naturally occurring amino acid residues and still retain the functional property of being a peptide "antigen."

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

Claim 56 is included in this rejection because it is unpredictable if adding flanking non-naturally occurring amino acid residues to the E75 peptide would produce a peptide antigen.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 56 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

This is a new ground of rejection necessitated by Applicant's amendment filed 7/1/10.

Claim 56 is indefinite in the recitation of "wherein the CTL epitope is E75".

E75 is SEQ ID NO: 2 or KIFGSLAFL, and as such, it contains no non-natural amino acid residues selected from among those recited in instant base claim 1. As such, it can not be both SEQ ID NO: 2 and the modified epitope recited in instant base claim 8.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 8, 20-22, 45, 46 and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by Carter, Darrick *et al* (FASEB J., Database Accession No.: PREV200100264480, March 8, 2001, Applicant's IDS reference "C55" filed 6/15/10) as evidenced by Anderson *et al* (Cancer Immunol. Immunother. 1999, 48: 401-410).

This is a new ground of rejection necessitated by Applicant's IDS filed 6/15/10.

Carter, Darrick *et al* teach a method for preparing a composition comprising a peptide antigen that is one of the E75 epitope heteroclitic peptide analogs with G4NVal or A7NLeu or F8HomoPhe (norvaline, norleucine and homophenylalanine, respectively).

Evidentiary reference Anderson *et al* teach that the E75 epitope is from Her2/neu tumor associated protein that is over-expressed in breast and ovarian tumors (especially abstract and last paragraph of reference).

Note that newly added claim 56 is not included in this rejection as the E75 peptide recited in said claim contains no non-natural amino acid residues, and base claim 8 recites that the CTL epitope comprises one or more non-natural amino acids. Applicant is advised that should the claims be amended to indicate that E75 is the unmodified epitope prior to substitution with non-natural amino acid residues, the art reference would apply to said claim.

Applicant is reminded that "what constitutes proper enablement of a prior art reference for purposes of anticipation under section 102…differs from the enablement standard under section 112." Rasmusson v. Smithkline Beechan Corp., Case Nos. 04-1192 (Fed. Cir. June 27, 2005)

13. Applicant is requested to clarify if phenyl glycine and isophenylalanine recited in instant base claim 8 are the same non-natural amino acid residues.

14. No claim is allowed.

15. Applicant's amendment filed 7/1/10 and Applicant's IDS filed 6/15/10 have necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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